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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,337	12/03/2003	Marguerite A. Cervin	GC778-2	8070

7590 07/10/2007

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,337	CERVIN ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-21,34-39,46-47 and 49-59* is/are pending in the application.

4a) Of the above claim(s) *34-39,46,47 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21,49-56,and 58-59* is/are rejected.

7)☒ Claim(s) *57* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 March 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *17 March 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Please note that the Examiner of this application has changed. This is the First Action on the Merits of U.S. Application 10/728,337 filed 3 December 2003, which claims priority to application PCT/US03/31544 filed 3 October 2003, which claims priority to U.S. Provisional Applications 60/416,166 and 60/374,931 filed 4 October 2002. Amendment to the specification to add the sequence listing filed 2 March 2007 has been received and entered. Replacement Drawings filed 2 March 2007 have been received and entered. Amendment to the claims filed 6 September 2006 has been received and entered. Claims 14-21, 34-39, 46-47 and 49-59 are pending. Claims 1-13, 22-33, 40-45 and 48 are cancelled. Claims 49-59 are new. Claims 34-39, 46-47 and 57 are withdrawn to non-elected subject matter. Claims 14-21, 49-56, and 58-59 are under examination.

Election/Restrictions

Claims 34-39, 46-47 and 57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6 September 2006.

Applicant's election with traverse of Group V in the reply filed on 6 September 2006 is acknowledged. The traversal is on the ground(s) that Applicant states that Groups V, VI, and VII have not acquired a separate status in the art as they are all classified in class 435, subclass 69.1. Applicant also traverses that there would be no

additional burden placed on the Examiner to search these groups together. This is not found persuasive because Group VII includes subject matter such as "a nucleic acid encoding a transketolase" and a nucleic acid encoding a "transaldolase" which would require a non-coextensive and thus burdensome search. In addition, Group VI is drawn to a method of a materially different design and would therefore require a non-coextensive and burdensome search.

New claims 49-56 and 58-59 are directed to subject matter of Group V. New claim 57 is drawn to the independent claim 46 and therefore belongs in the non-elected Group VI.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The restriction requirement is still deemed proper and is therefore made FINAL.

Specification

The disclosure is objected to because of the following informalities: The term "peremases" is a typographical error for "permeases" (p.32, line 24). Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (p.33, line 12). Applicant is required to delete

the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claim 57 is objected to because of the following informalities: Claim 57 is drawn to non-elected claim 46. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the **second paragraph** of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-21, 49-56, and 58-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "originally", in claim 14 is an indefinite term which renders the claim indefinite. The term "originally" is not defined by the claim, the specification does not provide a standard for ascertaining the metes and bounds of the term, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, the term "originally" could mean in the wild-type strain before the PTS mutations were introduced, or alternatively, could mean early in the growth cycle or under specific "original" culture conditions. Therefore, claim 14 is properly rejected under 112(2^{nd}).

The term "obtained from E.coli" in claims 16 and 17 is an indefinite term which renders the claims indefinite. The term "obtained from E.coli " is indefinite because it is not clear whether the galactose permease and glucokinase enzymes are required to be E. coli enzymes or, alternatively, could be heterologous enzymes that must merely be grown and isolated from E. coli. Therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and claims 16 and 17 are properly rejected under 112(2^{nd}).

The term "produced in a corresponding PTS bacterial cell" in claim 14 is indefinite because it is not clear whether a "corresponding PTS bacterial cell" is referring to the PTS^-/Glu^- cells used in step (a) (but lacking the addition of DNA transformation), or alternatively, whether the corresponding cell is referring to a PTS^+ cell. One of ordinary skill in the art would recognize that a cell phenotype, such as PTS, when written *without* a (+) or (-) symbol, by convention refers to the (+) or "wild-type" version of the cell. Therefore, the metes and bounds of the claim can not be determined as stated.

Claims 15-21, 49-56, and 58-59 are indefinite insofar as they depend from claim 14.

The following is a quotation of the **first paragraph** of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-21 and 51-56 and 58-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A review of the full content of the specification indicates that nucleotide sequences encoding promoter sequences or derivatives thereof and nucleotide sequences encoding amino acid sequences of a glucose assimilation protein capable of increasing the production of a desired product in a host cell are essential to the operation of the claimed invention.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." (See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

A review of the language of claims 14-21, 49-56 and 58-59 indicates that the claims are broadly drawn to a genus of nucleotide sequences comprising promoter sequences. In addition, claims 14-15, 18-21, 51, 53-55, and 58-59 are broadly drawn to a genus of nucleotide sequences encoding glucose assimilation proteins. Claims 16-17, 52, 56, and 58-59 are more specifically drawn to nucleotide sequences encoding galactose permease and/or glucokinase proteins. However, the specification does not explicitly describe any other glucose assimilation species in the claimed genus except for those in Figure 14 (SEQ ID NO's 25-27), or any other promoter sequences other than the trc promoter (see below). The specification does provide several NCBI database accession numbers to genes which have shown sequence identity to the E.coli glucokinase and provides some examples of glucose transporters in the literature and includes a hyperlink address to the TransportDB database. However, information provided by a hyperlink is not considered acceptable because the information provided at the hyperlink is subject to change. In addition, providing database accession numbers for nucleotide sequences, while providing addresses to potential nucleotide sequences of interest, are not considered as having provided the structural information pertaining to the sequences, because the nucleotide sequence associated with a given database accession number is subject to change. Neither the specification nor the prior art teaches the conserved structures in SEQ ID NO's 25-27 that are *essential* for the broad definition of promoter, "DNA flanking sequences corresponding to upstream (5') regions", glucose assimilation protein, galactose permease, or glucokinase. The only structures correlated with these *proteins* are the sequences of Figure 14 (SEQ ID NO's

25-27). In addition, the specification states: "As indicated above for glucose transporters, other glucose phosphorylating enzymes may be identified using the computer programs such as FASTA, GCG Pileup and BLASTA" (paragraph 0147, lines 1-3), which indicates that the applicant appears not to be in possession of the structures at the time of the invention. Therefore, given the breadth of the claim and the lack of further guidance, a person skilled in the art would conclude that applicants are not in possession of the claimed genus of glucose assimilation proteins.

Claims 14-21 and 49-56 and 58-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain bacterial host cells such as E. coli and for the nucleotide sequence of Figure 14, which is also the nucleotide sequences of SEQ ID NO's 25-27 (the DNA sequence of the GalP-ptrc DNA cassette as set forth in SEQ ID NO. 1) which includes the nucleotide sequence encoding for two examples of "glucose assimilation proteins", galactose permease and glucokinase, and includes the nucleotide sequence for the trc promoter and "flanking sequences" for that specific expression system, does not reasonably provide enablement for *all* types of bacterial cells, *all* nucleotide sequences for *any* promoter and/or "flanking sequences", or for *all* nucleotide sequences encoding for all "glucose assimilation proteins" or even more specifically for all galactose permeases or glucokinases. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Unpredictability of the art. The art in the area of heterologous promoters and expression of functional bacterial proteins is unpredictable. The research required to determine functional promoters and successful homologous recombination events in all types of bacterial cells in order to express all types of glucose assimilation proteins involves complex molecular modeling of the expression cassette molecule, cell conditions and oftentimes unknown RNA secondary structure considerations. It is difficult or impossible to *a priori* predict the exact promoter and flanking sequences required to express any type of glucose assimilation protein, and as such is an endeavor which requires extensive inventive research. Examples of the type of research required to identify a minimal promoter can be found in Kim et al (Kim et al. 1994, Plant Molecular Biology 24:105-117). For example, Kim et al demonstrates that the promoter element *essential* for its function could be very small Since neither the specification nor the prior art teaches all the motifs required for promoter activity, it is

not known which bases are indispensable for such promoter activity along the promoter region and which bases are not.

2) State of the art. The art with regard to expression in E. coli cells of E. coli galactose permease and E. coli glucokinase using the heterologous, exogenous trc promoter is described in the literature at the time of the invention (see prior art rejection below). Furthermore, the specification teaches the specific structures representing the -35 region (TTGACA) and the -10 region (TATAAT) of the trc promoter (instant specification, paragraph 0028 and FIG. 2). Given the general conserved structure for basic promoters in bacteria, it is reasonable to expect the same promoters to function in most bacteria. In addition, the term "promoter" is defined by the specification as: "a regulatory nucleic acid sequence that functions to direct transcription of a downstream gene or genes. A promoter according to the invention comprises two consensus regions. The first consensus region is centered about 10 base pairs (bp) upstream from the start site of transcription initiation and is referred to as the -10 consensus region (also the -10 box or Pribnow box). The second consensus region is centered about 35 bp upstream of the start site and is referred to as the -35 consensus box or sequence. A linker or spacer sequence is positioned between the consensus boxes and generally comprises 14 to 20 bp" (instant specification [paragraph 0056]. However, the art with regard to using *any* glucose assimilation protein (such as a mammalian protein) with any promoter sequence, in any bacterial host cell must be considered experimental.

3) Number of working examples. With the exception of the nucleotide sequence encoding the E.coli gal permease and glucokinase using the trc promoter in E.coli bacterial host cells, applicants present no working examples of the claimed invention.

4) Amount of guidance provided by applicants. Applicants present minimal guidance on the practicing of the claimed invention with any other molecules other than E.coli gal permease and E. coli glucokinase and the trc promoter. Applicants present no teachings on any other *essential* structural domains of any other glucose assimilation proteins, no teachings on the *essential* minimal promoter and 5'-flanking sequences required, and no teachings on the generation of any hybrid molecules comprising said promoters, 5'-flanking sequences and coding sequence for any/all types of glucose assimilation proteins. In addition, applicants do not provide guidance with regard to what type of promoter function any of these modified sequences might have and under what conditions they must be tested, since promoter function can depend on many factors such as cell type, developmental stage, environmental conditions, and presence of inducer. Furthermore, the specification did not indicate that the reverse complement DNA strand of SEQ ID No. 25-27 could also have promoter activity.

5) Scope of the claims. The claimed invention is extremely broad in scope. The invention reads on any promoter, any 5'-flanking sequences, any glucose assimilation proteins and any galactose permease and glucokinase proteins.

6) Nature of the invention. The invention involves complex, unpredictable, aspects of protein expression, carbohydrate metabolism, and design of novel hybrid molecules with unpredictable properties.

7) Level of skill in the art. The level of skill in the art is high; however, given the complex, unpredictable aspects of the invention, the lack of guidance presented by applicants, the lack of working examples and the broad scope of the invention, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

Given the analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have practiced essentially trial and error experimentation in order to try to practice the claimed invention. Said experimentation must be considered to be undue and excessive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-16, 49, 53 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Hernandez-Montalvo et al in "Characterization of sugar mixtures utilization by an Escherichia coli mutant devoid of the phosphotransferase system" in Appl Microbiol Biotechnol (2001) 57: 186-191, published online: 24 July 2001).

Claim 14 is directed to a method comprising: a) transforming a bacterial host cell having a PTS^-/Glu^- phenotype with a DNA construct comprising a promoter, wherein said DNA construct is chromosomally integrated into the PTS^-/Glu^- host cell replacing an endogenous promoter which is operably linked to a nucleic acid encoding a glucose assimilation protein; b) culturing the transformed bacterial host cell under suitable conditions; c) allowing expression of the glucose assimilation protein to obtain a host cell having a PTS^-/Glu^+ phenotype; and d) obtaining an increased amount of a desired product in the transformed bacterial host cell compared to the amount of the desired product produced in a corresponding PTS bacterial cell cultured under essentially the same culture conditions, wherein said desired product is selected from the group consisting of pyruvate, phosphoenolpyruvate (PEP), lactate, acetate, glycerol, ethanol, succinate and chorismate.

Hernandez-Montalvo et al teaches a method comprising: (a) transforming PTS^-/Glc^-, E. coli bacterial host cells with a plasmid (pCLvGalP1) carrying the *galP* gene under the control of the strong *trc* promoter (b) culturing the transformed cells (p.187, Materials and methods: see Fermenter cultures, lines1-10); (c) over-expressing the glucose assimilation protein, galactose permease, which allows for glucose transport and thus presenting a PTS^-/Glu^+ phenotype, and (d) obtaining an increase in the

desired product PEP. For example, Hernandez-Montalvo et al comtemplates increased production of PEP, ethanol and aromatic compounds (p.187, ¶ 2, lines 1-10, and p.190, ¶ 2, lines 1-20).

Therefore, Hernandez-Montalvo et al anticipates claims 14 and 15.

Furthermore, Hernandez-Montalvo et al teaches the method of claim 14 wherein the DNA construct includes an exogenous promoter and DNA flanking sequences corresponding to upstream (5') regions of the glucose assimilation protein (claim 53). For example, Hernandez-Montalvo et al transforms E. coli strains with the DNA plasmid pCLvGalP1, which is a pCL1920 derivative containing the *galP* gene controlled by the *trc* promoter (p.187, ¶ 4, lines 9-11). From previous results, it was determined that [14C]-xylose uptake in the PTS^- $Glucose^+$ strain was 36% higher than that observed for the wild-type or the PTS^- $Glucose^-$ strain. In order to test if GalP, which is involved in glucose transport in the PTS^- $Glucose^+$ strain, was also involved in the observed increase of [14C]-xylose uptake for this strain, the PTS^- $Glucose^-$ strain was transformed with a plasmid (pCLvGalP1) carrying the *galP* gene under the control of the strong *trc* promoter (P.190, ¶ 2, lines 1-15).

In addition, Hernandez-Montalvo et al teaches the method of claim 14, wherein the glucose assimilation protein is an E.coli galactose permease and further to wherein the galactose permease has at least 80% amino acid sequence identity to the galactose permease sequence set forth in Figure 14 (claims 16, 49 and 56) (Materials and methods, p.187, ¶ 4, lines 9-11).

Therefore, Hernandez-Montalvo et al teaches all the limitations of claims 14, 15, 16, 49, 53 and 56.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17,18-21, 50, 51, 52, 54, 55, 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hernandez-Montalvo et al as applied to claims 14, 15, 16, 49, 53 and 56 above, and further in view of Flores et al , "Analysis of Carbon Metabolism in *Escherichia coli* Strains with an Inactive Phosphotransferase System by ^{13}C Labeling and NMR Spectroscopy" in Metabolic Engineering Vol. 4, 124-137 (2002) (made of record in the IDS).

Claims 17, 50, 58 and 59 are directed to the method of claim 14 (described above), and are taught by Hernandez-Montalvo *et al.* for the reasons above. However, Hernandez-Montalvo *et al.* differs from the invention claimed in the instant claims 17, 50, 58 and 59, in that while it teaches the glucose assimilation protein, galactose permease, Hernandez-Montalvo *et al.* fails to teach wherein the glucose assimilation protein is an E.coli glucokinase (claims 17 and 50) and further to wherein the glucokinase has at least 70% amino acid sequence identity to the glucokinase set forth in Figure 14 (claim 58) and further to wherein the glucokinase has at least 95% amino acid sequence identity to the glucokinase set forth in Figure 14 (claim 59).

Flores *et al.* teaches wherein the glucose assimilation protein is an E.coli glucokinase which has at least 95% amino acid sequence identity to the glucokinase set forth in Figure 14, which reads on claims 17, 50, 58 and 59 (p.125, ¶ 2 and p.126, Table I)

One would have been motivated at the time the invention was made and it would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized glucokinase gene in the method taught in Hernandez-Montalvo *et al.* because Hernandez-Montalvo et al states that "internal glucose should be phosphorylated and the enzyme that can catalyze this reaction is glucokinase". Hernandez-Montalvo *et al* continues "partial characterization of these PTS- Glucose+ strains revealed that the level of glucokinase is higher than that present in the parent wild-type strains" and recites, "Interestingly, despite the absence of the PTS, characterization of these strains has shown that some of them are able to utilize other sugars, including PTS class I and II compounds not metabolized by PTS- strains." (p 187, ¶ 1, lines 5-16).

Both Hernandez-Montalvo *et al.* and Flores *et al.* are in the same field of endeavor (using PTS mutants to increase carbon flux in bacteria) and both are directed to the same problem sought to be solved (testing glucose assimilation proteins for their ability to rescue the PTS-/Glu- phenotype).

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of the E.coli glucose assimilation genes in DNA constructs with exogenous promoters for the purpose of expressing the E.coli proteins was routinely practiced at the time the teachings of Hernandez-Montalvo *et al.*, and Flores *et al.* were published.

In view of the foregoing, the method of claims 17, 50, 58 and 59, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a).*

Claims 51, 52, 54 and 55 are directed to the method of claim 14 (described above) and further comprising transforming the bacterial host cell with a second DNA construct comprising a promoter, wherein the second DNA construct is chromosomally integrated into the host cell replacing an endogenous promoter which is operably linked to a nucleic acid coding for a second glucose assimilation protein.

Hernandez-Montalvo *et al.* differs from the invention claimed in the claims 51, 52, 54 and 55, in that while it teaches the transformation of E.coli host cells with the glucose assimilation protein, galactose permease, and contemplates the importance of the glucokinase gene in this genetic system (above), Hernandez-Montalvo *et al.* fails to teach transforming the bacterial host cell with a second DNA construct comprising a promoter, wherein the second DNA construct is chromosomally integrated into the host cell replacing an endogenous promoter which is operably linked to a nucleic acid coding for a second glucose assimilation protein.

Flores *et al.* teaches expressing both the galactose permease and the glucokinase but fails to teach DNA transformation.

One would have been motivated at the time the invention was made and it would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized a second DNA construct comprising a promoter, wherein the second

DNA construct is chromosomally integrated into the host cell replacing an endogenous promoter which is operably linked to a nucleic acid coding for a second glucose assimilation protein because Flores et al taught both the galactose permease and glucokinase genes to increase the carbon flux in a PTS-/Glu+ phenotype and Hernandez-Montalvo et al taught the transformation of the galactose permease gene and trc promoter. It would be prima facie obvious to use a similar second DNA construct containing the glucokinase gene and trc promoter in addition to the galactose permease construct as a means of expressing the glucokinase gene in this genetic system. Both Hernandez-Montalvo *et al.* and Flores *et al.* are in the same field of endeavor (using PTS mutants to increase carbon flux in bacteria) and both are directed to the same problem sought to be solved (testing glucose assimilation proteins for their ability to rescue the PTS-/Glu- phenotype).

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of the E.coli glucose assimilation genes in DNA constructs with exogenous promoters for the purpose of expressing the E.coli proteins was routinely practiced at the time the teachings of Hernandez-Montalvo *et al.*, and Flores *et al.* were published.

In view of the foregoing, the method of claims 51, 52, 54 and 55, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a).*

Claims 18-21 are directed to the method of claim 14 (above). Hernandez-Montalvo et al anticipates the method of claim 14, but fails to explicitly state wherein the desired products are chorismate, succinate, ethanol, and glycerol, which read on claims 18-21 respectively.

Flores et al anticipates these products and teaches the increase in the carbon flux in an E. coli PTS^-/Glc^+ strain compared to a PTS^-/Glc^- strain which results in increased PEP, pyruvate, and DAHP. Flores et al also recites increasing the carbon flux through the malic enzymes, and the products glucose, acetate, lactate and ethanol (p.126, ¶3, lines 1-2) and glycerol (p.126, ¶4, lines 1-2). Because succinate is a component of the citric acid cycle it is an inherent product of increased pyruvate. Likewise, chorismate is an inherent product of an increase in its precursor, DAHP.

Although Hernandez-Montalvo et al did not explicitly cite all of these products, one would have been motivated to expect these products in the method of Hernandez-Montalvo et al because, for example, Hernandez-Montalvo et al contemplates increased production of PEP, ethanol and aromatic compounds (p.187, ¶ 2, lines 1-10, and p.190, ¶ 2, lines 1-20) and recites "industrial interest in PTS- Glucose+ strains comes from the expected increase in metabolic availability of the precursor molecule PEP" (p.187, ¶ 2, lines 1-3) .

Both Hernandez-Montalvo *et al.* and Flores *et al.* are in the same field of endeavor (using PTS mutants to increase carbon flux in bacteria) and both are directed

to the same problem sought to be solved (using glucose assimilation proteins for their ability to rescue the PTS-/Glu- phenotype and increase yield of carbon products).

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the desired products of an altered PTS system were known at the time Hernandez-Montalvo *et al.* and Flores *et al.* were published.

In view of the foregoing, the method of claims 18-21, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)*.

It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (scope of enablement) and 35 USC 102(b) and 103(a). While these rejections may seem contradictory, they are not because each is based upon a different legal analysis, i.e. sufficiency of the disclosure of the instant application to support claims under 35 USC 112, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783 (CCPA 1969)).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert whose telephone number is 571-270-3053. The examiner can normally be reached on Monday-Friday, 7:30 AM-5:00 PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully submitted,

Catherine S. Hibbert/AU1636

DAVID GUZO
PRIMARY EXAMINER